was obtained in 42% yield, mp 95.5–96°; unstable; not analyzed; transformed into **10** at once.

(*RS*)-**6-Chloro-2-quinoxalineepoxyethane** (**10**) was obtained in 70% yield, ligroin (bp 66–75°), 93–94°.

(*RS*)-α-(**Di-*n*-alkylaminomethyl**)-**6-chloro-2-quinoxaline-methanols** (**11**).—Data in Table I.

**Acknowledgment.**—The authors are indebted to Mr. John Oatis, Jr., for his skilled technical assistance, and to Drs. Sweeney and Strube of WRAIR for helpful advice.

## Synthesis and Antimicrobial Activity of 5,7-Dichloroquinoline-8-thiol and Its Derivatives

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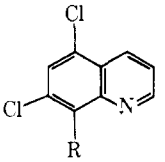
*Received March 16, 1970*

8-Hydroxyquinoline (oxine) and several of its derivatives are effective against Gram-positive and Gram-negative bacteria, and pathogenic fungi. In addition, halogenated 8-quinolinols are active against protozoa. Albert, *et al.*,[1] determined the minimal bacteriostatic concentrations of 8-quinolinol, 5-chloro-8-quinolinol, 7-chloro-8-quinolinol, and 5,7-dichloro-8-quinolinol, and showed that the chloro derivatives were superior to oxine against certain organisms.

Certain derivatives of the thio analog of 5,7-dichloro-8-quinolinol have now been prepared, and their bacteriostatic actions against various organisms determined. Although the tendency of 5,7-dichloroquinoline-8-thiol itself to undergo oxidation to the disulfide appears to be less than that of quinoline-8-thiol, under the test conditions considerable oxidation occurred, both with the dichlorothiol and also with its Na salt.

**Chemistry.**—5,7-Dichloroquinoline (**1a**) was prepared by the method of Elderfield and Kreuger,[2] and converted into its 8-sulfonyl chloride (**1c**) either by direct chlorosulfonation or indirectly by the action of $PCl_5$ on the 8-sulfonic acid (**1b**). Reduction of the sulfonyl



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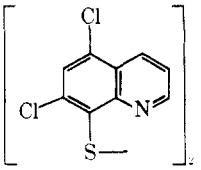

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a, R = H
b, R = $SO_3H$
c, R = $SO_2Cl$
d, R = SH

chloride with $SnCl_2$ in concd HCl gave tin 5,7-dichloroquinoline-8-thiolate, which in the presence of NaOH and $I_2$ yielded 5,7-dichloro-8-quinolyl disulfide (**2**). Alkaline reduction of the disulfide gave 5,7-dichloroquinoline-8-thiol (**1d**). The pmr spectrum of 5,7-dichloroquinoline displayed a doublet at τ 1.97, attributable[3] to the 8 proton *meta* coupled to the 6 proton ($J$ = 2 Hz). That chlorosulfonation had proceeded in the 8 position was confirmed by the absence of the 8 proton in the spectrum of the sulfonyl chloride, and presence of the 6 proton as a singlet.

Attempts to synthesize the 5,7-dichloroquinoline-8-thiol system by chlorination of quinoline-8-thiol, its benzoate or 8-quinolyldisulfide proved unsuccessful, and these reactions are under further investigation.

**Biological Evaluation.**—The antimicrobial activities of 5,7-dichloroquinoline-8-thiol and several related compounds were screened against both Gram-positive and Gram-negative bacteria, and yeasts. The following organisms were utilized: *Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus faecalis* (Gram-positive), *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative), *Saccharomyces cerevisiae*, and *Candida albicans* (yeasts).

The compounds were dissolved in DMSO and added to nutrient agar (for bacteria) and sabouraud agar (for yeasts) to give a concentration range of 200–6.25 μg/ml. The organisms were streaked onto the surface of the agar plate and minimum inhibiting concentration recorded after 24 and 48 hr. 8-Quinolinol was screened as a control.

The results (see Table I) indicate a broad spectrum for tin 5,7-dichloroquinoline-8-thiolate, while showing its antimicrobial activity to be less than that of 8-quinolinol under the evaluation conditions applied.

## Experimental Section[4]

**5,7-Dichloroquinoline-8-sulfonic Acid.**—A solution of 5,7-dichloroquinoline (3 g) in 25% oleum (15 ml) was heated at 140° for 40 hr, then added dropwise to crushed ice (50 g). The pptd acid was filtered, washed with $H_2O$, and recrystd from $H_2O$ to give the sulfonic acid (3.25 g) as prisms, mp 300°. *Anal.* ($C_9H_5Cl_2NO_3S$) C, H, N.

**5,7-Dichloroquinoline-8-sulfonyl Chloride** (**a**).—The temperature of an intimately ground mixture of 5,7-dichloroquinoline-8-sulfonic acid (1 g) and $PCl_5$ (1.2 g) was gradually increased to 160°, then held there for 1 hr. $POCl_3$ was distd and the residue was added portionwise to crushed ice (20 g). The mixture was ground up and extracted ($C_6H_6$) and the extract was washed successively with aq $NaHCO_3$ and $H_2O$, then dried, and evaporated. Recrystallization of the residue from EtOAc gave product (0.5 g) as prisms: mp 140–141°; pmr ($CDCl_3$) τ 0.34 (quadruplet, $J$ = 4.5 and 1.7 Hz) ($H_2$), 1.27 (quadruplet, $J$ = 8.5 and 1.7 Hz) ($H_4$), 2.17 ($H_6$), 2.25 (quadruplet, $J$ = 8.5 and 4.5 Hz) ($H_3$) ppm. *Anal.* ($C_9H_4Cl_3NO_2S$) C, H, N.

(**b**).—A solution of 5,7-dichloroquinoline (10 g) in chlorosulfonic acid (30 ml) was heated at 140° for 40 hr then cooled and added dropwise with stirring to crushed ice (250 g). The mixture was filtered and the residue was washed ($H_2O$), then triturated with 5% aq $NaHCO_3$, and refiltered. Recrystallization of the dried residue from EtOAc gave a product (6.2 g), identical with the above sample.

**Tin 5,7-Dichloroquinoline-8-thiolate.**—A solution of $SnCl_2 \cdot 2H_2O$ (12 g) in concd HCl (25 ml) was added at 0° to a solution of 5,7-dichloroquinoline-8-sulfonyl chloride (4 g) in concd HCl (25 ml). The yellow ppt was stirred at 0° for 1 hr then allowed to stand overnight at 0° before filtration. The residue was triturated with $H_2O$ and the ppt (3.6 g) was filtered, and re-

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(2) R. C. Elderfield and G. L. Kreuger, *J. Org. Chem.*, **17**, 358 (1952).

(3) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Braunschweig, (1969) p 308.

(4) Melting points were determined on a Gallenkamp MF.370 apparatus and are uncorrected. Pmr spectra were determined on a Varian A60A spectrometer with TMS as internal reference. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Table I
Minimum Inhibiting Concentration (μg/ml)

| Derivative | *Staphylococcus aureus* | | *B. cereus* | | *Streptococcus faecalis* | | *K. coli* | | *P. aeruginosa* | | *Saccharomyces cerevisiae* | | *C. albicans* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 24 hr | 48 hr | 24 hr | 48 hr | 24 hr | 48 hr | 24 hr | 48 hr | 24 hr | 48 hr | 24 hr | 48 hr | 24 hr | 48 hr |
| 8-Quinolinol | 18.75 | 18.75 | 18.75 | 18.75 | 18.75 | 18.75 | 25.0 | 25.0 | 37.5 | 37.5 | 6.25 | 6.25 | 9.3 | 9.3 |
| Tin 5,7-dichloroquinoline-8-thiolate | 50.0 | 50.0 | 37.5 | 37.5 | 50.0 | 50.0 | 37.5 | 37.5 | 37.5 | 37.5 | 50.0 | 50.0 | 50.0 | 50.0 |
| Sodium 5,7-dichloroquinoline-8-thiolate | >128 | >128 | | | | | >128 | >128 | | | >128 | >128 | >128 | >128 |
| 1d | 102.5 | 200 | | | | | 102.5 | 128 | | | 128 | 128 | 128 | 128 |
| 2 | >200 | >200 | | | | | >200 | >200 | | | >200 | >200 | >200 | >200 |

crystd from DMSO to give the Sn salt as prisms, mp 340–342°. *Anal.* ($C_{18}H_8Cl_4N_2S_2Sn$) Sn.

**Sodium 5,7-Dichloroquinoline-8-thiolate.**—The above Sn salt (1 g) was stirred in a solution of NaOH (1.5 g) in $H_2O$ (25 ml) overnight. The Na salt was filtered, washed with $H_2O$, and dried. Recrystallization of the dried residue (0.55 g) from EtOH gave the sodium salt as yellow needles, mp 280° dec.

**5,7-Dichloro-8-quinolyl Disulfide.**—To a solution of NaOH (1.5 g) and $I_2$ (0.25 g) in $H_2O$ (100 ml) was added finely ground tin 5,7-dichloroquinoline-8-thiolate (1.4 g). The mixture was stirred overnight and then filtered and the residue was thoroughly washed with $H_2O$. Recrystallization of the dried residue from dioxane gave product (0.30 g) as yellow prisms, mp 219–220°. *Anal.* ($C_{18}H_8Cl_4N_2S_2$) C, H, N.

**5,7-Dichloroquinoline-8-thiol.**—To a stirred suspension of the above disulfide (0.25 g) in oxygen-free MeOH (25 ml) were added successively, solutions of NaOH (0.65 g) in $H_2O$ (5 ml) and glucose (0.65 g) in $H_2O$ (5 ml). The mixture was stirred and heated under reflux for 3 hr, before evapn of the MeOH. The mixture was filtered and the residual Na salt was dissolved in $H_2O$ (25 ml). $CO_2$ was passed through the solution for 10 min, and the white ppt was filtered and dried *in vacuo*. Recrystallization from MeOH gave the thiol (0.1 g) as needles, mp 102–103°; pmr spectrum as expected. *Anal.* ($C_9H_5Cl_2NS$) C, H, N.

**Acknowledgment.**—The authors thank Mr. L. S. Bark (University of Salford) for a Sn analysis on tin 5,7-dichloroquinoline-8-thiolate.

# Structural Modification Studies of 3-Piperonylsydnone. 2. Synthesis of Piperonyl-Substituted Hydantoin, Thiohydantoin, Thiazolidinedione, Rhodanine, Imidazolinone, and Related Compounds[1]

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*Received February 16, 1970*

The antimalarial activity of a mesoionic compound, 3-piperonylsydnone (I), against *Plasmodium berghei* was reported.[2] Preliminary structure–activity relationship studies[2,3] revealed the importance of the piperonyl moiety for the antimalarial activity for compounds of this type. The mode of action of I is still unknown. One possible explanation for the many interesting biological activities exhibited



I

by the sydnones[4,5] is that these compounds may interfere with the biochemical role of amino acids. It is certainly not improbable for 3-piperonylsydnone to act as an amino acid antagonist since the compound itself was prepared from an N-substituted amino acid (*N*-piperonylglycine).[2] Consequently, syntheses of certain piperonyl derivatives containing a hydantoin (IIa),

(1) This investigation was supported by Contract DA-49-193-MD-2749 with the U. S. Army Medical Research and Development Command. This paper is Contribution No. 767 from the Army Research Program on malaria.

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